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| ORGANON USA, INC. PATENT DEPARTMENT 56 LIVINGSTON AVENUE ROSELAND, NJ 07068 | | | EXAMINER LUKTON, DAVID | |
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/698,238

Applicant(s)

WAN ET AL.

Examiner

David Lukton

Art Unit

1654

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 14 December 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 24-39 is/are pending in the application.
- 4a) Of the above claim(s) 32 and 37-39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 24-31 and 33-36 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

Pursuant to the directives of the response filed 10/4/07, claim 24 has been amended. Claims 24-39 remain pending.

Applicants have requested clarification as to whether or not the "election of species" requirement has been made final. In response, the requirement has indeed been made final. The examiner also acknowledges that a petition of the requirement remains a viable option for applicants.

Applicants have also questioned the withdrawal of claims 37-39. In the restriction requirement mailed 5/16/06, applicants were required to elect one of the following: (i) a method in which the proteins are purified or (ii) a method in which the proteins are not purified. Applicants responded (filed 6/16/06) that the proteins are not "further" purified. This was taken then, and remains taken as an indication that no purification of the proteins, beyond that required of claim 24 (as of 10/31/03) was (or is) required. Applicants have conceded that there is justification in withdrawing claim 32, since it recites the phrase "purifying the proteins". At the same time, applicants are arguing in effect that one can take a bacterial lysate and perform steps which result in a 95% yield of protein, and that this can be achieved without any purification. Whether this is true or not depends on how narrowly one wants to construe the term "yield". According to one interpretation, the term at issue would mean that nearly all impurities have been removed, so that the purity of the proteins is 95%. According to another interpretation, the 95% yield does not refer to

purity at all, but merely that portion of the proteins which is not lost as a result of passing through diatomaceous earth. At the present time, the first of these possibilities is assumed. If claim 24 is found to be allowable in its present form, the issue of withdrawal of claims 37-39 will prove to be moot.



Applicants' arguments filed 10/4/07 have been considered and found not persuasive. Claims 24-31 and 33-36 are examined in this Office action.

The abbreviation **DE** represents "diatomaceous earth".



Claims 24-25 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of USP 6,995,246. Although the conflicting claims are not identical, they are not patentably distinct from each other; there is overlap of the claimed subject matter. Claim 1 of the patent is subgeneric to claim 24 of the instant application. Applicants have requested deferral of this issue until allowable subject matter is identified.



Claims 24-25 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 24 of copending application Serial No. 10/698230. Although the conflicting claims are not identical, they are not patentably distinct from each other. Applicants have requested deferral of this issue until allowable subject

matter is identified.



Claim 35 is objected to because of a typographical/grammatical error. This claim recites the following phrase: "...wherein the lysate **is a** comprises". As is evident, there is a minor error here.



Claims 24-31 and 33-36 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are drawn to a method of removing suspended particles from a solution. However, given the meaning of the term "solution", this would appear not to be possible. Consider the following hypothetical claims:

100. A method of removing water from an anhydrous solution comprising

101. A method of removing sodium chloride from distilled water comprising

102. A method of removing particles from a liquid mixture, wherein all components are dissolved in the liquid, and as such there are no particles to remove.

Each of the foregoing claims (100-101) represent examples that are analogous to the present claims. If one has a vial that contains a "solution", that vial does not contain a suspension. Similarly, if one has a vial that contains a suspension, that vial does not contain a solution. Thus, claim 24 represents a contradiction in terms. If it is really

true that one has a “solution” that contains soluble proteins and DNA, then that solution cannot contain particles. Of course, a composition can contain particles, as would a suspension or a mixture or a cell lysate. But as matters currently stand, the claims are indefinite.

In response to the foregoing, applicants have argued essentially that the protein chemist of ordinary skill generally equates the term “solution” with a “particulate suspension”. However, these two terms do not refer to the same physical state; there is really no overlap between the two. If one takes a solution, and adds particular matter so as to generate a suspension of the particles, one no longer has a solution. In actually, the claimed method comprises the step of filtering a suspension through DE so as to generate a solution.



The following is a quotation of 35 USC, §103 which forms the basis for all obviousness rejections set forth in the Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not

commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 24-31, 33, 34, 36 are rejected under 35 U.S.C. §103 as being unpatentable over Hsu (USP 6,008,328) in view of Hennen (USP 6,468,534) or Colpan (USP 6,274,371).

As indicated previously, Hsu discloses a method for obtaining KGF from lysed bacteria which expressed the KGF. Cell lysis is also disclosed (e.g., col 11, line 10+). Hsu also discloses (col 12, line 25+) removal of endotoxins. Also disclosed (col 11, line 19) is the use of a "filter aid" to clarify the cell lysate. Also disclosed (e.g., col 2, line 56+) is blocking of cysteine sulfhydryl groups. Hennen discloses (col 10, line 41) that diatomaceous earth is useful for preventing clogging of filters when filtering protein solutions that contain precipitates. Hennen does not disclose a method which comprises removing suspended particles from a lysate, and which method also comprises reducing the amount of DNA and endotoxins. Colpan discloses a method for removal of cellular debris comprising a filtration step. A preferred filtration aid (col 2, line 31+) is diatomaceous earth. Colpan does not disclose a method which comprises removing suspended particles from a lysate, and which method also comprises reducing the amount of DNA and endotoxins. Thus, a practitioner of the Hsu invention would purify KGF from lysed bacteria by using various methods including a filtration aid. Hsu discloses the claimed invention, except that there is no specific teaching that the "filter aid" should be diatomaceous earth. However, a protein chemist in possession of Colpan or

Hennan would have recognized that if a filter aid is used, diatomaceous earth would have been effective for this purpose.

In response, applicants have argued that the references do not recite the phrase “highly purified” diatomaceous earth. However, the claims impose no limitations on what this might mean. In any case, most commercial suppliers of the product would provide the diatomaceous earth with sufficient purity to qualify. Applicants have also argued that they have provided an “exhibit A”. However, no such exhibit has been received in the instant application.

As for claims 37-39, these are withdrawn, but if rejoined, the rejection would apply to these claims as well. Since isolation of a protein is the ultimate objective (rather than isolation of DNA), a practitioner of the Hsu process would have been motivated to maximize the yield of the KGF.

The rejection is maintained.



Claims 24-31, 33, 34, 36 are rejected under 35 U.S.C. §103 as being unpatentable over Hsu (USP 6,008,328) in view of Hennen (USP 6,468,534) or Colpan (USP 6,274,371) further in view of Shiuh (USP 5,656,568).

The disclosures of Hsu, Hennen and Colpan were indicated previously. Shiuh discloses highly purified DE. Thus, it would have been obvious to use the DE of Shiuh for the advantages cited therein.



Claims 24-31, 34, 36 are rejected under 35 U.S.C. §103 as being unpatentable over Lander (US 2001/44136).

As indicated previously, Lander discloses a method of purifying plasmid DNA that includes the use of diatomaceous earth to clarify cell lysates. In addition, Lander is replete with references to diatomaceous earth for removal of debris from cell lysates. In addition, proteins are mentioned in table 4 (page 14) and also at least one time in each of the following paragraph numbers: 11, 39, 40, 46, 48, 66, 67, 70, 71, 73, 83 and 98.

In response to the foregoing, applicants have argued that the claimed method excludes isolation of plasmid DNA. However, this assertion is not true; the claims encompass many different embodiments, one of which is isolation of plasmid DNA. Applicants have also argued that the examiner believes that the claimed method excludes the isolation of proteins. This assertion is also not true; isolation of proteins is one of the many processes that are encompassed.

Claim 24 also encompasses the following ("claim 103"):

103. A method for removing suspended particles from a first aqueous mixture that contains proteins, genomic DNA and plasmid DNA, wherein the method comprises the following steps:

a) filtering said first aqueous mixture through DE to produce a second aqueous mixture that contains proteins, genomic DNA and plasmid DNA; and

b) removing a portion of the proteins and a portion of the genomic DNA from said second aqueous mixture to produce a third aqueous mixture that contains plasmid DNA, but which still contains detectable amounts of proteins and genomic DNA.

Now consider what Lander teaches. See, for example paragraph 0070, paragraph 0071, paragraph 0073, and paragraphs 0078-0083 (see also table 4). What Lander teaches is a process which can be described by the following claim ("claim 104")

104. A process which comprises the following steps:

a) obtain a cell lysate, and then clarify it with DE to produce an aqueous mixture of proteins, genomic DNA and plasmid DNA;

b) remove genomic DNA from the mixture of step (a) to produce a mixture which is enriched in plasmid DNA but which still contains residual proteins and

c) continue with other steps.

Applicants have attempted to draw focus to the ultimate objective of Lander, which is to obtain plasmid DNA. While it may be true that this is the ultimate objective of the reference, the fact remains that there is far more to the analysis. As indicated above in claim 104, Lander teaches a process, such that if one performs part of the process, one

meets the requirements of the instant claims. The biochemist of ordinary skill who is reproducing the Lander process for obtaining plasma DNA would be well aware that proteins would still be present after removing a portion of the DNA and endotoxins.

This realization would exist, notwithstanding the fact that the practitioner of the Lander invention might have little interest in isolating and further using the proteins which are produced. The instant claims encompass many different final objectives. Claim

24 encompasses the possibility of ultimately isolating plasma DNA and discarding proteins and genomic DNA. Claim 24 encompasses the possibility of isolating lipids from the cell lysates, and discarding proteins and DNA.

Despite the ultimate objectives of Lander, this reference discloses a process which comprises the steps recited in the instant claims.

The rejection is maintained.



Claims 24-31, 34, 36 are rejected under 35 U.S.C. §103 as being unpatentable over Theodossiou, I. (*Bioprocess Engineering* **16**(3), 175-183, 1997) in view of Luo (USP 6,365,147) or Marquet (USP 5,561,064).

As indicated previously, Theodossiou discloses methods of using DE as a filtration aid in the recovery of plasmid DNA from cell lysates. Although the emphasis is on isolation of plasmid DNA, the reference also discloses (e.g., table 5, page 182) that

protein is present after the filtration. Theodossiou also discloses that some loss of DNA occurred as a result of the filtration. Theodossiou does not disclose removal of endotoxins.

Luo discloses (e.g., col 4, line 7) the desirability of, and methods for removal of endotoxins from plasmid DNA. Luo does not discuss the use of diatomaceous earth to clarify cell lysates. Marquet ('064) discloses (e.g., col 5, line 25+) the desirability of, and methods for removal of endotoxins from plasmid DNA. Marquet ('064) does mention the use of diatomaceous earth to clarify cell lysates, but does not provide an extensive discussion of this subject.

Theodossiou meets all of the limitations of claim 24, except for the requirement that endotoxins be removed. The secondary references teach the artisan of ordinary skill how to remove endotoxins. Thus, it would have been obvious to one of ordinary skill to follow the process described by Theodossiou, and then to remove endotoxins from the plasmid DNA.

In response to the foregoing, applicants have argued that since the objective of Theodossiou is the use of diatomaceous earth as a filtration aid in the recovery of plasmid DNA from cell lysates, it is impossible to meet the requirements of the instant claims. The examiner's arguments here are much the same as in the §103 rejection over Lander ('136), i.e., that in the process of purifying plasmid DNA according to the references, one

is indeed meeting the requirement for reduction in the amount of DNA and endotoxin.

The fact that a practitioner of the Theodossiou might want to merely discard all of the proteins at the end of the process does not undermine the validity of this rejection. The instant claims do not require isolating or purifying the proteins. It is sufficient that a reference teaches, as an intermediate step, a process in which DNA and endotoxins are reduced, as long as there is still some protein present in the mixture at that point.

Applicants have argued that in one embodiment Theodossiou removes more than 95% of the proteins. This may be true, but (a) Theodossiou affirmatively recites that some protein remained after reducing the level of DNA and endotoxins, and (b) instant claim 24 does not exclude the possibility that 95+% of the proteins originally present have been removed.

The rejection is maintained.



Claims 24-31, 34, 36 are rejected under 35 U.S.C. §103 as being unpatentable over Colpan (USP 6,274,371) in view of Theodossiou, I. (*Bioprocess Engineering* **16**(3), 175-183, 1997).

As indicated previously, Colpan discloses a method for isolating DNA from cell culture, such as a bacterial cell culture (e.g., col 1, line 7+; col 2, line 34+; col 4, line 36+). The reference calls for lysing the cells and then filtering them. A preferred

filtering material is diatomaceous earth (e.g., col 2, line 7-8; col 2, line 31+; col 4, line 36+). Colpan does not explicitly state that protein will be present in the lysate, however, the cell biologist of ordinary skill is aware that cells contain proteins. In addition, Colpan does not disclose reducing the amount of DNA and does not explicitly state that the amount of endotoxins will be reduced. Theodossiou discloses (e.g., page 182, table 5) that if a solution containing DNA is filtered through diatomaceous earth, some reduction in the amount of DNA will occur. Theodossiou does not disclose a method which comprises reducing the amount of endotoxins.

Applicants have made essentially the same arguments here as in the traversal over Theodossiou in view of Luo ('147) and Theodossiou in view of Marquet ('064). The examiner does the same.



THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). The practice of automatically extending the shortened statutory period an additional month upon filing of a timely first response to a final rejection has been discontinued by the Office. See 1021 TMOG 35.

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED AND ANY EXTENSION FEE PURSUANT TO 37 CFR 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR

RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 571-272-0952. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang, can be reached at (571)272-0562. The fax number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

A handwritten signature in black ink, appearing to read 'David Lukton', with a stylized, cursive script.

DAVID LUKTON, PH.D.
PRIMARY EXAMINER